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Semen quality in men with epilepsy receiving anti-seizure medications: a case-control study

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Abstract

Background

Epilepsy and anti-seizure medications (ASMs) may adversely affect male fertility, although the extent of this impact remains unclear. This study aimed to evaluate semen quality in men with epilepsy and to explore the potential effects of commonly used ASMs, particularly valproate and levetiracetam. This single-centre case–control study was conducted at a tertiary referral centre involving 16 men with a confirmed diagnosis of epilepsy who had been receiving ASM therapy for at least six months and 16 age-matched healthy controls. Demographic and epilepsy-related clinical data were collected following informed consent. Semen samples were obtained at the Advanced Reproductive Centre and analyzed according to standard laboratory guidelines.

Results

Men with epilepsy demonstrated significantly lower sperm viability (56.6% vs 74.0%; $p = 0.015$), total motility (56.6% vs 71.3%; $p = 0.031$), and progressive motility (42.8% vs 55.4%; $p = 0.025$) compared with healthy controls. No significant differences were observed in sperm count or morphology between these two groups. Subgroup analyses did not demonstrate statistically significant differences between ASM groups, although patients receiving valproate tended to exhibit poorer semen quality.

Conclusion

Men with epilepsy appear to have impaired sperm function, particularly in terms of motility and viability, while sperm production may remain relatively preserved. These findings suggest that epilepsy treated with ASMs may negatively affect semen quality. Further prospective multi-centre studies are recommended to confirm these associations.

Background

Epilepsy is a chronic neurological disorder characterized by an enduring predisposition to generate epileptic seizure. It is associated with neurobiological, cognitive, psychological, and social consequences. It is commonly understood as a disorder involving recurrentand unprovoked seizures (1). Epilepsy affects more than 50 million people worldwide (2). In Malaysia, the prevalence of epilepsy has been reported to be up to 7.8 per 1,000 population (3).

Anti-seizure medications (ASMs) are the cornerstone of epilepsy treatment, with more than 70% of patients achieving seizure control with pharmacological therapy (4). The choice of ASM therapy is largely guided by seizure type (5). Focal seizures are defined as epileptic activity originating within networks limited to one hemisphere, whereas generalized seizures originate from bilaterally distributed networks involving both cortical and subcortical structures (6). First-line treatment options for focal seizures include carbamazepine, lamotrigine, and oxcarbazepine (7). Sodium valproate, lamotrigine, and topiramate are treatment options for generalized seizures. Newer agents such as levetiracetam and perampanel are also commonly used as either first- or second-line treatments. (7).

Sodium valproate, lamotrigine, and levetiracetam are broad-spectrum ASMs that exert their antiepileptic effects through different mechanisms. Sodium valproate increases GABAergic activity, blocks sodium and calcium channels, and limits glutamate activity (8). Lamotrigine stabilizes neuronal membranes by blocking voltage-gated sodium channels and inhibiting glutamate release. Levetiracetam uniquely binds to synaptic vesicle protein 2A (SV2A), thereby modulating neurotransmitter release (9).

Sodium valproate is associated with adverse effects such as hair loss, tremors, weight gain, hepatotoxicity, and pancreatitis. Carbamazepine is associated with serious cutaneous adverse reactions, including toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS). Levetiracetam may cause somnolence, dizziness, and behavioural changes such as irritability or hostility (7). Perampanel is generally considered safe, with reported adverse effects including drowsiness and hyponatraemia (10). These adverse effects are well recognized and are routinely considered during clinical monitoring.

In current clinical practice, the choice of ASM is no longer based solely on seizure type. Neurologists increasingly consider individual patient factors such as age, sex, comorbidities, reproductive potential, and long-term safety. This shift has been driven in part by the strong association between sodium valproate and teratogenic effects, including up to a 10% risk of neural tube defects and facial abnormalities, as well as a 30–40% risk of developmental delay and autism spectrum disorder among children exposed in utero (11). While the endocrine and reproductive effects of valproate have been well described in women, including menstrual irregularities and polycystic ovary syndrome, its impact on male reproductive function remains less clearly established and continues to be debated (12).

Reproductive health is an important consideration because epilepsy is a chronic condition and many patients require long-term exposure to ASMs. Epilepsy itself may contribute to alterations in the hypothalamic–pituitary–gonadal axis, potentially mediated by limbic system involvement and disruption of gonadotropin-releasing hormone (GnRH) pulsatility. In addition, ASMs may affect sex hormone levels through hepatic enzyme induction or direct gonadal effects, thereby contributing to reproductive dysfunction (13).

Male fertility is an important aspect of quality of life, particularly among individuals of reproductive age living with chronic neurological conditions such as epilepsy. Semen analysis is a key laboratory assessment of male reproductive potential. In this study, the term “semen quality” refers to the overall assessment of semen based on standard semen analysis parameters rather than a single measurement. These parameters include semen volume, sperm concentration, total sperm count, sperm motility, progressive motility, sperm viability, sperm morphology, pH, and viscosity.

Semen volume reflects the amount of ejaculate produced, while sperm concentration and total sperm count reflect the number of sperm present per milliliters and per ejaculate, respectively. Sperm motility refers to the ability of sperm to move, whereas progressive motility reflects the proportion of sperm moving forward effectively. Sperm viability represents the proportion of live spermatozoa, and sperm morphology describes the structural appearance of sperm, including head, mid-piece, and tail characteristics. Physical properties such as pH and viscosity are also assessed as part of semen analysis (14). Therefore, semen quality should be interpreted by evaluating individual semen quality rather than as a single aggregate outcome. Any abnormality in these parameters may have implications for male reproductive potential.

Several studies have reported that men with epilepsy may experience gonadotropic hormonal dysregulation, impaired semen quality, sexual dysfunction, and reduced fertility potential. Hamed et al. demonstrated dose related reductions in sperm count and motility among patients receiving sodium valproate, along with an increased prevalence of abnormal sperm morphology (15). Similarly, Xu et al. evaluated sodium valproate and levetiracetam in Chinese Han men with epilepsy and reported altered reproductive hormone profiles, increased sperm morphological abnormalities in the sodium valproate group, and reduced sperm motility in both treatment groups (16).

Despite emerging evidence, studies evaluating semen quality in men with epilepsy remain limited and often involve small sample sizes, heterogeneous medication exposure, and variable study designs. Data from the Malaysian population are particularly scarce. Therefore, this study was conducted to compare semen quality between men with epilepsy receiving ASMs and age matched healthy controls. As this was a cross-sectional, case–control study, it was not designed to independently differentiate the effects of epilepsy itself from the effects of ASM exposure. However, the findings may provide preliminary local data on semen quality in men with epilepsy receiving ASMs and may assist clinicians in counselling male patients with epilepsy regarding fertility and long-term reproductive health.

Methods

Study Design

This was a single-centre, case-control study conducted between June 2025 and February 2026 at Hospital Canselor Tuanku Muhriz (HCTM), Kuala Lumpur following institutional ethical approval. Patients aged 18 to 50 years, with a confirmed diagnosis of epilepsy and on ASM for at least six months, were screened and recruited from the Outpatient Neurology Clinic HCTM.

Patients with a prior history of infertility and other general medical conditions that could affect sperm parameters, such as diabetes mellitus, chronic kidney disease, and chronic liver disease, were excluded from this study. Individuals with genetic diseases, recreational drug use, and use of hormonal therapies were also excluded.

Sample size and data collection

The sample size was determined based on the previous study by Hamed et al., comparing semen quality between patients with epilepsy receiving valproate and healthy controls.[14] The required sample size was nine patients per arm. Of the 253 patients screened, 26 met the eligibility criteria and agreed to participate. However, 10 patients dropped out, giving a final number of 16 patients. Aged matched, healthy males (n = 16) were recruited into the control arm (Fig. 1).

Demographic and clinical data were obtained from the electronic medical records. Participants were referred to the Advanced Reproductive Centre (ARC) at HCTM for semen collection. Semen samples were collected and processed according to WHO 2021 recommendations. Participants were advised for two to seven days of sexual abstinence, complete ejaculate collection and avoidance of lubricants that could

affect the semen quality. The samples were analyzed by trained medical laboratory technologists using standardized laboratory procedures. They were blinded to the participants' group allocation.

Semen analysis can be divided into three components: macroscopic characteristics, quantitative and functional parameters, and morphology. Macroscopic characteristics include semen volume, pH, and viscosity. Quantitative and functional parameters include total sperm count, sperm concentration, motility, progressive motility, non-progressive motility, immotility, and viability. Morphological assessment includes normal forms and specific structural defects such as head, mid-piece, tail, and mixed defects. It is important to note that male fertility should not be interpreted as a single aggregate measure. It is determined by evaluating each individual component. Hence, changes in any of these parameters may affect male fertility.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 30.0. Continuous variables were assessed for normality using the Shapiro–Wilk test and visual inspection of histograms and Q–Q plots and are presented as mean ± standard deviation or median (interquartile range), as appropriate; categorical variables are presented as frequencies and percentages. Univariate analyses were performed to assess associations between epilepsy, antiseizure medication use, and semen characteristics, with statistical significance defined as $p < 0.05$.

Results

The mean age of the epilepsy patients was 36.4 ± 10.0 years, predominantly Chinese (11, 68.8%). Most participants were employed (14, 87.5%), and 8 (50.0%) had attained tertiary-level education. Three-quarter (12, 75.0%) had never smoked, while 11 (68.8%) were social drinkers. The mean BMI among the epilepsy patients was 25.6 ± 4.5 kg/m². The mean duration since diagnosis of epilepsy was 15.5 ± 10.9 years. Most patients had generalized epilepsy (12, 75.0%). Nine (56.3%) had epilepsy of unknown aetiology, six (37.5%) had a structural cause, and one (6.3%) had epilepsy secondary to infection.

A total of 13 patients (81.3%) were not drug-resistant. The majority (7, 43.8%) had a seizure frequency of more than 12 months. More than half (9, 56.3%) demonstrated abnormal epileptiform discharges on EEG and seven (43.8%) had normal imaging findings. On average, patients were prescribed 1.8 ± 1.2 ASMs. The majority were on sodium valproate (10, 62.5%), followed by levetiracetam (11, 68.8%), lamotrigine (3, 18.8%), and carbamazepine (3, 18.8%). The mean maximum doses were 827.8 ± 405.5 mg, 1772.7 ± 1190.9 mg, 183.3 ± 125.8 mg, and 400.0 ± 0.0 mg, respectively (Table 1).

Table 2 describes the semen analysis in patients with epilepsy and the control group. For the macroscopic characteristics of semen, namely viscosity, volume, and pH, there were no significant differences between the epilepsy and control groups. Regarding the quantitative and functional parameters, semen viability and total motility showed significant differences between the two groups (p=0.015 and p=0.031, respectively). Progressive sperm motility also demonstrated a significant difference between the groups (p=0.025). There were no significant differences between the two groups with regard to total sperm count, non-progressive motility, and sperm immotility.

There was a significant difference between the epilepsy and control groups in terms of midpiece defects (p=0.046). Meanwhile, the other morphological characteristics showed no significant differences. The majority of our patients were treated with valproate (62.5%) and levetiracetam (68.8%) as seen in Table 2. However, the small sample size limited the ability to perform drug-specific analyses. Additionally, due to insufficient data on treatment duration, overlap in drug exposure could not be excluded in the analysis.

There was no significant association between the macroscopic characteristics of semen, quantitative and functional sperm parameters, and sperm morphology when comparing patients with epilepsy on valproate and those not on valproate (Table 3). Similarly, there was no significant association between the macroscopic characteristics of semen, quantitative and functional sperm parameters, and sperm morphology when comparing patients with epilepsy on levetiracetam and those not on levetiracetam (Table 4).

Table 5 summarizes the correlation between semen analysis parameters and epilepsy related characteristics, which includes duration of diagnosis epilepsy type, aetiology of epilepsy, drug response, seizure frequency, EEG findings and imaging finding. Overall, most semen parameters did not show statistically significant associations with epilepsy characteristics (p>0.05). However, a few notable findings were observed. For macroscopic characteristics, semen volume demonstrated a statistically significant association with duration of diagnosis (p=0.036), but not with other epilepsy-related variables. In terms of quantitative and functional sperm parameters, including total sperm count, viability, and motility (progressive, non-progressive, and immotile), no significant correlations were identified with any of the epilepsy characteristics studied.

Regarding sperm morphology, the percentage of normal forms was significantly associated with duration of diagnosis (p=0.039). Additionally, mid-piece defects showed significant associations with both aetiology (p=0.043) and imaging findings (p=0.039). Mixed defects were significantly associated with seizure frequency (p<0.001). No significant associations were observed for head defects or tail defects. Interestingly, smoking had a significant association with the total sperm count (p<0.001), whereas alcohol intake showed a statistical significance (p=0.039) in changes in non-progressive motility of sperm. There was a significant association noted between obesity and progressive motility of the sperm (p=0.036).

Discussion

This study demonstrated that men with epilepsy had significantly reduced sperm viability and motility compared with healthy controls, while sperm concentration, total sperm count, and morphology were not significantly different between groups. Specifically, sperm viability was lower in the epilepsy group compared to controls, while total motility and progressive motility were also significantly reduced. In contrast, total sperm count and normal morphology did not differ significantly. These findings suggest that epilepsy and ASMs predominantly affect sperm function rather than spermatogenesis.

A significant reduction in sperm viability was observed among men with epilepsy compared to controls. This indicates that a lower proportion of spermatozoa remained viable in the epilepsy group, reflecting impaired membrane integrity and increased cellular damage. This finding is consistent with previous studies demonstrating impaired semen quality in men with epilepsy. Xu et al. reported reduced sperm viability and altered reproductive parameters in men receiving ASMs (16). The reduction in viability may be explained by increased oxidative stress, which leads to lipid peroxidation of sperm membranes and subsequent cell death. In addition, disruption of the hypothalamic–pituitary–gonadal axis may impair spermatogenesis and sperm maturation, further contributing to reduced viability (16).

Sperm motility was also significantly reduced in men with epilepsy. Total motility was lower in the epilepsy group, and progressive motility was similarly reduced, as compared to the control group. These findings indicate that not only are fewer sperm motile, but the proportion capable of forward progression is also significantly impaired. This observation is supported by a previous study done by Hamed et al., who demonstrated that valproate use was associated with reduced sperm motility in a dose-dependent manner (15). Similarly, Xu et al. reported decreased motility in men treated with valproate and levetiracetam (16). The impairment in motility may be attributed to mitochondrial dysfunction, as sperm motility is highly dependent on ATP production. Oxidative stress may further exacerbate this by damaging mitochondrial structures, resulting in reduced energy availability and impaired sperm movement (15).

In contrast, no significant difference was observed in sperm concentration or total sperm count between the epilepsy and control groups. Although the epilepsy group demonstrated a numerically lower sperm count, this did not reach statistical significance. This suggests that spermatogenesis may be relatively preserved in men with epilepsy, and that the primary effect is on sperm function rather than production. Previous studies have reported inconsistent findings, with some demonstrating reduced sperm counts in patients receiving anti-seizure medications, while others have reported normal counts despite functional impairment(15–17). The preservation of sperm count in this study may indicate that functional abnormalities, such as reduced motility and viability, may occur earlier than measurable changes in sperm production.

No significant difference was observed in sperm morphology between the epilepsy and control groups, suggesting that the proportion of structurally normal sperm was comparable. Previous studies have reported variable findings regarding morphology. Hamed et al. observed increased abnormal morphology in patients receiving valproate, whereas other studies did not demonstrate significant differences (15). The absence of a significant difference in this study may be related to the relatively small sample size or variability in medication exposure. It is also possible that morphological abnormalities develop later in the disease course or with prolonged exposure to anti-seizure medications.

Interestingly, a significant difference was observed in mid-piece defects between the groups, with a higher proportion noted in the control group. This finding is contrary to the overall trend of poorer semen quality in the epilepsy group and may not reflect a true biological association. This discrepancy may be due to sampling variability, small sample size, or measurement variability in morphological assessment. As the mid-piece is critical for mitochondrial function, abnormalities in this region would typically be expected to correlate with reduced motility (18). However, given the direction of this finding, it should be interpreted with caution and may not be clinically significant.

Subgroup analysis comparing patients receiving valproate and non-valproate regimens did not demonstrate statistically significant differences in semen quality. However, patients on valproate showed a trend toward poorer sperm function, with lower sperm viability, motility, and normal morphology compared with those not receiving valproate, although these differences did not reach statistical significance. Despite the lack of statistical significance, these findings are in keeping with previous studies. Hamed et al. reported dose-

dependent reductions in sperm count and motility among men receiving valproate (15),while Xu et al. demonstrated reduced motility and increased morphological abnormalities in patients exposed to valproate (16). The absence of statistically significant differences in this study may be attributed to the relatively small sample size and heterogeneity of ASM exposure, including the use of polytherapy, which may confound the isolated effects of individual drugs.

Similarly, no statistically significant differences were observed between levetiracetam and non-levetiracetam groups, and no clear directional pattern was evident across semen quality. Patients receiving levetiracetam demonstrated comparable semen quality, with no consistent trend toward deterioration, suggesting that levetiracetam may have a less pronounced effect on sperm function. This is consistent with existing literature, which generally reports a more favourable reproductive profile for levetiracetam compared to valproate (19). However, given the limited sample size and variability in treatment regimens, definitive conclusions regarding drug-specific effects cannot be made.

A few isolated associations were identified, including semen volume and normal morphology with duration of diagnosis, as well as mid-piece defects with aetiology and imaging findings, and mixed defects with seizure frequency. However, these findings were not consistent across other semen parameters and are unlikely to represent clinically meaningful relationships. Overall, the lack of consistent correlations supports the concept that reproductive dysfunction in epilepsy is multifactorial, involving a combination of disease-related, hormonal, and treatment-related factors rather than being solely determined by seizure severity. This is consistent with previous studies, which have demonstrated variable and inconsistent associations between epilepsy characteristics and reproductive dysfunction (20).

As shown in Table 5, most semen parameters in this cohort of 16 men with epilepsy did not demonstrate significant associations with epilepsy-related characteristics. Total sperm count, viability, and motility were not significantly associated with duration of diagnosis, epilepsy type, seizure frequency, EEG findings, or imaging abnormalities. Overall, this supports the view that reproductive dysfunction in epilepsy is likely multifactorial rather than determined by disease severity alone (21).

Among the significant findings, semen volume was associated with duration of diagnosis, and normal morphology was also associated with duration of diagnosis. As the mean duration of epilepsy in this cohort was 15.5 ± 10.9 years, these findings may suggest that chronic disease or prolonged ASM exposure could influence selected semen quality over time. This is in keeping with previous studies showing that men with epilepsy receiving long-term ASM therapy may demonstrate altered semen quality and reproductive dysfunction (22). However, these associations should be interpreted cautiously, as they were observed in a small sample and were not accompanied by consistent changes in the main functional semen outcomes.

Mid-piece defects were significantly associated with aetiology and imaging findings, while mixed defects were associated with seizure frequency. Nevertheless, these results should be interpreted with caution because the subgroup sizes were small and no consistent associations were seen across the major functional semen parameters. Although mid-piece abnormalities are biologically relevant given the role of sperm mitochondria in motility and energy production, these observations are best considered exploratory (23).

Smoking was significantly associated with total sperm count. This finding is consistent with previous literature showing that cigarette smoking is associated with reduced sperm count and poorer semen quality, with more pronounced effects seen in moderate and heavy smokers (24). Alcohol intake was significantly associated with non-progressive motility. Although previous studies have generally assessed sperm motility as a whole rather than its subtypes, existing reviews suggest that alcohol consumption adversely affects sperm motility and broader semen quality (25).

Lastly, our study also showed that obese patients had a significant reduction in sperm progressive motility. These findings are supported by recent systematic reviews by Li et al. and Ji et al (26, 27). Obesity-related endocrine factors, such as reduced testosterone and increased estrogen levels, the presence of oxidative stress, as well as mitochondrial dysfunction, may affect the efficacy of sperm forward movement (28). This effect may be modest when taking into account other confounding factors, namely lifestyle and additional metabolic factors (29).

Strength of this study

This study has several strengths. Firstly, the case–control design with the inclusion of a healthy control group allowed for direct comparison of semen quality, strengthening the ability to attribute observed differences specifically to epilepsy and ASM exposure. Secondly, strict inclusion and exclusion criteria were applied to eliminate known confounding factors affecting semen quality, such as chronic medical illnesses, hormonal therapy, genitourinary conditions, and substance use, thereby enhancing the internal validity of the study.

Thirdly, semen analysis was performed using standardized WHO 2021 reference criteria by trained medical laboratory technologists, ensuring accuracy, reproducibility, and reliability of measurements. In addition, participants were given standardized pre-analysis instructions, including abstinence period and sample handling and processing under ARC laboratory under HCTM, which minimized procedural variability. Furthermore, detailed clinical data regarding epilepsy characteristics and ASM exposure were collected, allowing for subgroup analysis and a more comprehensive evaluation of potential contributing factors. Finally, this study addresses a relatively underexplored area, particularly within the Malaysian population, thereby contributing valuable local data to the existing literature on male reproductive health in epilepsy.

Limitations

Several limitations ought to be acknowledged in the current study. Firstly, the sample size was relatively small with only 16 participants in each group, which may have limited the statistical power to detect significant differences, particularly in subgroup analyses involving specific ASMs. This is especially relevant for the valproate and levetiracetam subgroup analyses, where the small number of participants limits the ability to draw firm conclusions regarding drug-specific effects. This may have contributed to the absence of statistically significant findings despite observable trends in certain semen quality.

Secondly, this study was conducted at a single tertiary centre, which may limit the generalizability of the findings to the wider population. In addition, recruitment of participants posed a significant challenge. Due to the sensitive nature of semen collection, some potential control participants were reluctant to participate because of embarrassment, cultural and social sensitivities, and concerns regarding potential abnormal results. Work commitments also limited participation among healthy individuals.

Similarly, recruitment among patients with epilepsy was affected by practical and clinical factors. Some patients, particularly those with intellectual disabilities, were unable to comply with semen collection procedures. Others who were willing to participate experienced difficulty in producing samples, possibly due to psychological stress or performance-related anxiety. These factors may have introduced selection bias and limited the representativeness of the study population.

In addition, patients in this study were exposed to heterogeneous ASM regimens, including polytherapy, making it difficult to isolate the effects of individual drugs on semen quality. The cross-sectional nature of semen assessment, with semen analysis performed at a single time point, also limits the ability to establish causality or assess temporal changes in semen quality.

Another important limitation is that the control group was matched according to age only. BMI matching was not performed due to recruitment limitations and a small pool of eligible healthy controls. As BMI is a known factor that may influence semen quality, the lack of BMI matching may have introduced residual confounding. Hormonal profiles, including testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), were not evaluated, which limits further understanding of the underlying endocrine mechanisms contributing to reproductive dysfunction.

Lastly, although standardized procedures were followed, variability in abstinence duration and sample collection conditions may have introduced measurement variability. All participants were advised to maintain a WHO recommended abstinence period of two to seven days prior to semen collection; however, the exact abstinence duration was not systematically recorded for all participants and was not compared between groups.

Conclusion

In conclusion, this study shows that men with epilepsy tend to have poorer sperm function, particularly in terms of reduced motility and viability, while sperm count and overall morphology appear to be relatively preserved. This suggests that epilepsy and/or its treatment may affect the quality and function of sperm more than the actual production of sperm.

The lack of consistent associations between semen quality and epilepsy-related factors also suggests that reproductive dysfunction in epilepsy is likely multifactorial, rather than being solely related to disease severity. Although no statistically significant differences were found in subgroup analyses of ASMs, the observed trends, especially among patients on valproate, are in line with previous studies and may still be clinically relevant.

Overall, these findings highlight the importance of considering reproductive health in men with epilepsy, especially in those of reproductive age. Greater awareness and appropriate counselling should be encouraged. Further studies with larger sample sizes and longitudinal follow-up are needed to better understand the underlying mechanisms and the long-term impact on fertility.

We recommend that future studies on ASM and male fertility be conducted as multi-centre studies with larger sample sizes to improve statistical power. Furthermore, to minimize dropout rates, both patients and their partners or family members should be adequately informed about the importance of the study during the consent process to ensure proper sample collection and analysis. In addition, the presence of a partner or parent during sample collection should be encouraged to ensure correct collection methods and to provide moral support.

Abbreviations

ARC	Advanced Reproductive Centre
ASM/ASMs	Anti-seizure medication(s)
ATP	Adenosine triphosphate
BMI	Body mass index
EEG	Electroencephalography
FSH	Follicle-stimulating hormone
GABA	Gamma-aminobutyric acid
GnRH	Gonadotrophin-releasing hormone
HCTM	Hospital Canselor Tuanku Muhriz
IBM	International Business Machines
LH	Luteinizing hormone
p	Probability value
pH	Potential of hydrogen
Q-Q	Quantile-quantile
SJS	Steven Johnson syndrome
SPSS	Statistical Package for the Social Sciences
SV2A	Synapse vesicle protein 2A
TEN	Toxic epidermal necrolysis
WHO	World Health Organization

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Research and Ethics Committee of Faculty of Medicine, Universiti Kebangsaan Malaysia (Research Code: FF-2025-292). Written informed consent was obtained from all participants prior to enrolment in this study.

Consent for publication

All authors agreed to the publication to this study.

Availability of data and materials

The datasets used in this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contribution

KV: data curation, project administration, methodology, formal analysis and writing of the original draft.

RR: methodology, formal analysis, review and editing of the manuscript, and supervision.

CSK: conceptualized the study, methodology, formal analysis, review and editing of the manuscript, and supervision.

HJT, AKK: methodology, review and editing of the manuscript, and supervision.

RH: statistical analysis and review of writing

NSJ, QWT, HYK data curation and project administration

All authors read and approved the final manuscript.

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Tables

Table 1. Characteristics of patients with epilepsy. (N=16)

Variables	Value
Demographic Characteristics	
Age, in years	36.4 ± 10.0
Race, n (%)	
Chinese	11 (68.8)
Indian	5 (31.3)
Employment status, n (%)	
Employed	14 (87.5)
Unemployed	2 (12.5)
ADL, n (%)	
Independent	16 (100.0)
Dependent	0 (0.0)
Marital Status, n (%)	
Single	10 (62.5)
Married	6 (37.5)
Education, n (%)	
Primary	0 (0.0)
Secondary	8 (50.0)
Tertiary	8 (50.0)
Smoker, n (%)	
Never	12 (75.0)
Former	3 (18.8)
Light	0 (0.0)
Medium	1 (6.3)
Heavy	0 (0.0)
Alcohol Intake, n (%)	11 (68.8)
Height, cm	170.8 ± 4.3
Weight, kg	74.7 ± 13.1
BMI, kg/m^2	25.6 ± 4.5
Underweight	0 (0.0)
Normal	4 (25.0)
Pre-obese	6 (37.5)
Obese	6 (37.5)
Epilepsy Characteristics	
Duration of diagnosis, years	15.5 ± 10.9
Types, n (%)	

Focal	4 (25.0)
Generalised	12 (75.0)
Unknown	0 (0.0)
Aetiology, n (%)	
Structural	6 (37.5)
Genetic	0 (0.0)
Infection	1 (6.3)
Metabolic	0 (0.0)
Immune	0 (0.0)
Unknown	9 (56.3)
Response to ASM, n (%)	
Non-drug-resistant	13 (81.3)
Drug-resistant	3 (18.8)
Seizure frequency, n (%)	
Daily	0 (0.0)
Weekly	1 (6.3)
Monthly	2 (12.5)
3 monthly	1 (6.3)
6 monthly	5 (31.3)
12 months and above	7 (43.8)
EEG findings, n (%)	
Normal	7 (43.8)
Abnormal discharges	9 (56.3)
Imaging, n (%)	
Normal	9 (56.3)
Abnormal	7 (43.8)
Anti-seizure medications	
Number of ASMs	1.8 ± 1.2
Types	
Sodium Valproate, n (%)	10 (62.5)
Average max dose, mg	827.8 ± 405.5
Duration, years	12.2 ± 9.1
Levetiracetam, n (%)	11 (68.8)
Average max dose, mg	1772.7 ± 1190.9
Duration, years	8.4 ± 9.1
Lamotrigine, n (%)	3 (18.8)
Max dose, mg	183.3 ± 125.8
Duration, years	13.7 ± 11.9

Carbamazepine, n (%)	3 (18.8)
Average max dose, mg	400.0 ± 0.00
Duration, years	11.7 ± 14.2
Others, n (%)	
Topiramate	2 (12.5)
Clonazepam	2 (12.5)
Perampanel	1 (6.3)
Clobazam	1 (6.3)
Phenobarbitone	0 (0.0)
Phenytoin	0 (0.0)

Continuous values are presented as mean ± standard deviation for normally distributed data. ADL = Activities of daily living, BMI = Body mass index, ASMs = Anti-seizure medications; EEG = Electroencephalography.

Table 2. Semen analysis in patients with epilepsy and control groups.

Semen Analysis	Epilepsy (n=16)	Control (n=16)	*p*-value
Macroscopic Characteristics			
Viscosity, n (%)			-
Normal	16 (100.0)	16 (100.0)	
Abnormal	0 (0.0)	0 (0.0)	
Semen volume, n (%)			1.000*
Normal	11 (68.8)	11 (68.8)	
Abnormal	5 (31.2)	5 (31.2)	
pH, n (%)			-
Normal	16 (100.0)	16 (100.0)	
Abnormal	0 (0.0)	0 (0.0)	
Quantitative and Functional Parameters			
Total sperm count, mL	119.6 ± 142.3	158.9 ± 133.4	0.426&
Viability, %	56.6 ± 22.4	74.0 ± 15.0	**0.015&**
Total motility, %	56.6 ± 22.4	71.3 ± 13.0	**0.031**&
Rapidly progressive[b]	0.0 ± 0.0	0.0 ± 0.0	-
Progressive	42.8 ± 20.8	55.4 ± 13.5	**0.025&**
Non-progressive	13.8 ± 9.3	15.9 ± 5.4	0.224&
Immotile	37.1 ± 19.4	28.3 ± 12.5	0.067&
Morphology, %			
Normal forms	2.2 ± 1.6	2.4 ± 1.4	0.321&
Head defect	60.1 ± 28.4	52.8 ± 30.9	0.247&
Mid-piece defect	13.7 ± 11.3	24.8 ±17.9	**0.046&**
Tail defect	17.0 ± 15.3	20.0 ± 15.8	0.605&
Cytoplasmic droplet[b]	0.0 ± 0.0	0.0 ± 0.0	-
Pinhead[b]	0.0 ± 0.0	0.0 ± 0.0	-
Mix defects	0.8 ± 2.3	0.0 ±0.0	0.074&

Continuous values are presented as mean ± standard deviation for normally distributed data.

* = Chi-Square test, & = Independent T-test, "-" = No statistical test performed as variable is constant in both groups, [b] = Not observed in both groups.

Table 3. Semen analysis in patients with epilepsy on valproate and non-valproate.

Semen Analysis	Valproate (N=10)	Non-valproate (N=6)	*p*-value
Macroscopic Characteristics			
Viscosity, n (%)			-
Normal	10 (100.0)	6 (100.0)	
Abnormal	0 (0.0)	0 (0.0)	
Semen volume, n (%)			0.588[#]
Normal	6 (60.0)	5 (83.3)	
Abnormal	4 (40.0)	1 (16.7)	
pH, n (%)			-
Normal	10 (100.0)	6 (100.0)	
Abnormal	0 (0.0)	0 (0.0)	
Quantitative and Functional Parameters			
Total sperm count, mL	120.1 ± 166.2	118.7 ± 105.0	0.985[&]
Viability, %	50.4 ± 23.8	66.8 ± 16.9	0.163[&]
Motility, %	50.4 ± 23.8	66.8 ± 16.9	0.163[&]
Rapidly progressive[b]	0.0 ± 0.0	0.0 ± 0.0	-
Progressive	39.0 ± 21.7	49.0 ± 19.5	0.370[&]
Non-progressive	11.4 ± 6.2	17.8 ± 12.5	0.187[&]
Immotile	39.6 ± 21.1	33.0 ± 17.0	0.528[&]
Morphology, %			
Normal forms	1.9 ± 1.3	2.7 ± 2.1	0.372[&]
Head defect	53.8 ± 32.2	70.5 ± 18.4	0.268[&]
Mid-piece defect	14.7 ± 13.7	12.0 ± 6.4	0.601[&]
Tail defect	18.4 ± 16.3	14.7 ± 14.7	0.653[&]
Cytoplasmic droplet[b]	0.0 ± 0.0	0.0 ± 0.0	-
Pinhead[b]	0.0 ± 0.0	0.0 ± 0.0	-
Mix defects	1.1 ± 2.8	0.3 ± 0.8	0.535[&]

Continuous values are presented as mean ± standard deviation for normally distributed data.
[#] = Fisher's Exact Test, [&] = Independent T-test, "-" = No statistical test performed as variable is constant in both groups, [b] = Not observed in both groups.

Table 4. Semen analysis in patients with epilepsy on levetiracetam and non-levetiracetam.

Semen Analysis	Levetiracetam (N=11)	Non-Levetiracetam (N=5)	*p*-value
Macroscopic Characteristics			
Viscosity, n (%)			-
Normal	11 (100.0)	5 (100.0)	
Abnormal	0 (0.0)	0 (0.00	
Semen volume, n (%)			1.000[#]
Normal	8 (72.7)	3 (60.0)	
Abnormal	3 (27.3)	2 (40.0)	
pH, n (%)			-
Normal	11 (100.0)	5 (100.0)	
Abnormal	0 (0.0)	0 (0.00	
Quantitative and Functional Parameters			
Total sperm count, mL	85.8 ± 85.6	193.8 ± 218.2	0.338[&]
Viability, %	57.0 ± 23.2	55.6 ± 23.2	0.912[&]
Motility, %	57.0 ± 23.2	55.6 ± 23.2	0.912[&]
Rapidly progressive[b]			
Progressive	42.1 ± 20.0	44.2 ± 24.9	0.858[&]
Non-progressive	14.9 ± 10.4	11.4 ± 6.5	0.501[&]
Immotile	33.8 ± 17.6	44.4 ± 23.2	0.328[&]
Morphology, %			
Normal forms	2.1 ± 1.7	2.4 ± 1.5	0.734[&]
Head defect	55.3 ± 29.3	70.6 ± 25.8	0.333[&]
Mid-piece defect	14.6 ± 11.4	11.8 ± 12.2	0.668[&]
Tail defect	18.0 ± 15.9	14.8 ± 15.4	0.713[&]
Cytoplasmic droplet[b]	0.0 ± 0.0	0.0 ± 0.0	-
Pinhead[b]	0.0 ± 0.0	0.0 ± 0.0	-
Mix defects	1.0 ± 2.7	0.4 ± 0.9	0.643[&]

Continuous values are presented as mean ± standard deviation for normally distributed data.
[#] = Fisher's Exact Test, [&] = Independent T-test, "-" = No statistical test performed as variable is constant in both groups, [b] = Not observed in both groups.

Table 5. Correlation between semen analysis with epilepsy characteristics and lifestyle factors.

Semen Analysis	Duration of diagnosis	Epilepsy Type	Aetiology	Drug Response	Seizure frequency	EEG	Imaging	Smoking	Alcohol	Obesity
Macroscopic Characteristics										
Semen volume, n(%)	**0.036**[$]	0.547[#]	0.538[#]	0.214[#]	0.239[#]	1.000[#]	0.596[#]	0.999[#]	0.345[#]	0.124[$]
Quantitative and Functional Parameters										
Total sperm count, mL	0.373[$]	0.710[&]	0.722[a]	0.470[&]	0.845[a]	0.265[&]	0.344[&]	**<0.001**[$]	0.985[&]	0.168[$]
Viability, %	0.855[$]	0.241[&]	0.543[a]	0.821[&]	0.213[a]	0.863[&]	0.404[&]	0.416[&]	0.051[&]	0.075[$]
Motility, %	0.855[$]	0.241[&]	0.543[a]	0.821[&]	0.213[a]	0.863[&]	0.404[&]	0.472[&]	0.054[&]	0.070[$]
Progressive	0.936[$]	0.246[&]	0.486[a]	0.550[&]	0.136[a]	0.632[&]	0.236[&]	0.429[&]	0.238[&]	**0.036**[$]
Non-progressive	0.531[$]	0.824[&]	0.949[a]	0.873[&]	0.787[a]	0.509[&]	0.705[&]	0.401[&]	**0.039**[&]	0.718[$]
Immotile	0.593[$]	0.540[&]	0.361[a]	0.738[&]	0.221[a]	0.365[&]	0.731[&]	0.459[&]	0.779[&]	0.446[$]
Morphology, %										
Normal forms	**0.039**[$]	0.932[&]	0.188[a]	0.550[&]	0.542[a]	0.259[&]	0.926[&]	0.096[&]	0.369[&]	0.637[$]
Head defect	0.651[$]	0.889[&]	0.578[a]	0.777[&]	0.914[a]	0.479[&]	0.665[&]	0.353[&]	0.316[&]	0.860[$]
Mid-piece defect	0.619[$]	0.455[&]	**0.043**[a]	0.203[&]	0.606[a]	0.893[&]	**0.039**[&]	0.479[&]	0.736[&]	0.248[$]
Tail defect	0.729[$]	0.747[&]	0.065[a]	0.604[&]	0.697[a]	0.975[&]	0.126[&]	0.336[&]	0.766[&]	0.573[$]
Mix defects	0.788[$]	0.458[&]	0.410[a]	0.514[&]	**<0.001**[a]	0.435[&]	0.333[&]	0.221[&]	0.830[&]	0.573[$]

[$] = Pearson correlation, [#] = Fisher's Exact Test. [&] = Independent T-test, [a] = One-way ANOVA.

Figures

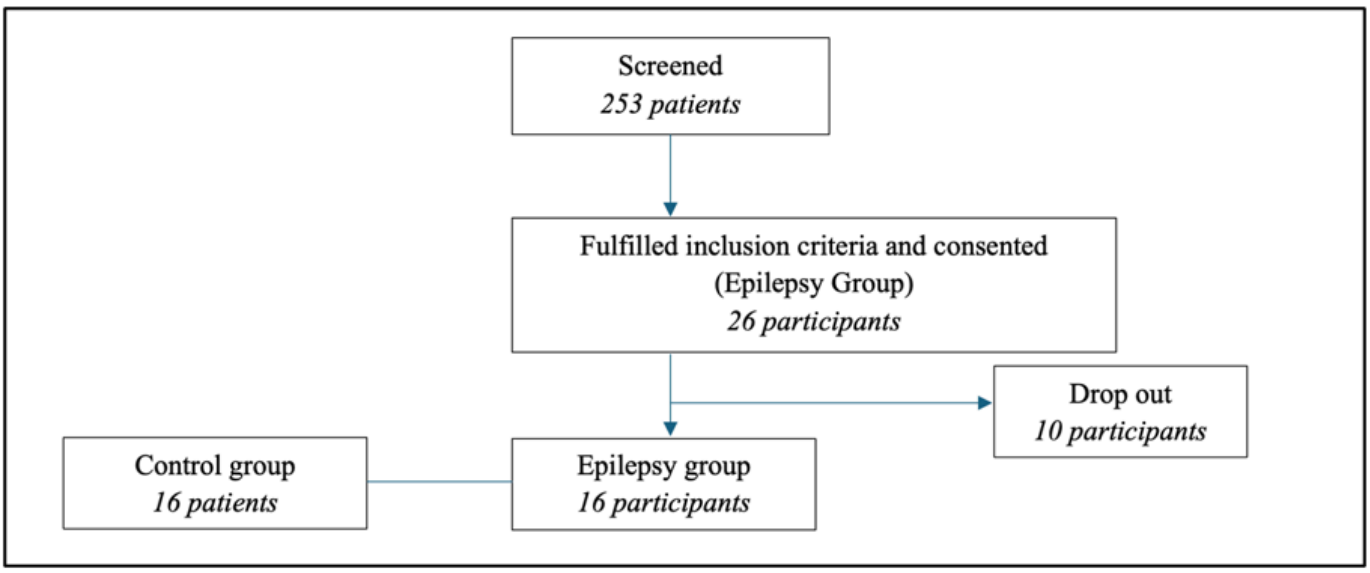

Figure 1

Flow chart for patient screening and recruitment